Na+/Ca2+ exchanger is a determinant of excitation-contraction coupling in human embryonic stem cell-derived ventricular cardiomyocytes.

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Public Summary:
In adult cardiomyocytes (CMs), the Na+/Ca2+ exchanger (NCX) is a well-defi ned determinant of Ca2+ homeostasis. Developmentally, global NCX knockout in mice leads to abnormal myofi brillar organization, electrical defects, and early embryonic death. Little is known about the expression and function of NCX in human heart development. Self-renewable, pluripotent human embryonic stem cells (hESCs) can serve as an excellent experimental model. However, hESC-derived CMs are highly heterogeneous. A stably lentivirus-transduced hESC line (MLC2v-dsRed) was generated to express dsRed under the transcriptional control of the ventricular-restricted myosin light chain-2v (MLC2v) promoter. Electrophysiologically, dsRed+ cells differentiated from MLC2vdsRed hESCs displayed ventricular action potentials (AP), exclusively. Neither atrial nor pacemaker APs were observed. While ICa-L, If, and IKr were robustly expressed, IKs and IK1 were absent in dsRed+ ventricular hESCCMs. Upon differentiation (7+40 to +90 days), the basal [Ca2+]i, Ca2+ transient amplitude, maximum upstroke, and decay velocities signifi cantly increased (P < 0.05). The ICa-L antagonizer nifedipine (1 μM) decreased the Ca2+ transient amplitude (to ~30%) and slowed the kinetics (by ~2-fold), but Ca2+ transients could still be elicited even after complete ICa-L blockade, suggesting the presence of additional Ca2+ infl ux(es). Indeed, Ni2+-sensitive INCX could be recorded in 7+40- and +90-day dsRed+ hESC-CMs, and its densities increased from −1.2 ± 0.6 pA/pF at −120 mV and 3.6 ± 1.0 pA/pF at 60 mV by 6- and 2-folds, respectively. With higher [Ca2+]i, 7+90-day ventricular hESC-CMs spontaneously but irregularly fi red transients upon a single stimulus under an external Na+-free condition; however, without extracellular Na+, nifedipine could completely inhibit Ca2+ transients. We conclude that INCX is functionally expressed in developing ventricular hESC-CMs and contributes to their excitation–contraction coupling.

Scientific Abstract:
In adult cardiomyocytes (CMs), the Na(+)/Ca(2+) exchanger (NCX) is a well-defined determinant of Ca(2+) homeostasis. Developmentally, global NCX knockout in mice leads to abnormal myofibrillar organization, electrical defects, and early embryonic death. Little is known about the expression and function of NCX in human heart development. Self-renewable, pluripotent human embryonic stem cells (hESCs) can serve as an excellent experimental model. However, hESC-derived CMs are highly heterogeneous. A stably lentivirus-transduced hESC line (MLC2v-dsRed) was generated to express dsRed under the transcriptional control of the ventricular-restricted myosin light chain-2v (MLC2v) promoter. Electrophysiologically, dsRed+ cells differentiated from MLC2vdsRed hESCs displayed ventricular action potentials (AP), exclusively. Neither atrial nor pacemaker APs were observed. While I(Ca-L), I(f), and I(Kr) were robustly expressed, I(Ks) and I(K1) were absent in dsRed+ ventricular hESCCMs. Upon differentiation (7+40 to +90 days), the basal [Ca(2+)](i), Ca(2+) transient amplitude, maximum upstroke, and decay velocities significantly increased (P < 0.05). The I(Ca-L) antagonizer nifedipine (1 microM) decreased the Ca(2+) transient amplitude (to approximately 30%) and slowed the kinetics (by approximately 2-fold), but Ca(2+) transients could still be elicited even after complete ICa-L blockade, suggesting the presence of additional Ca(2+) influx(es). Indeed, Ni(2+)-sensitive INCX could be recorded in 7+40- and +90-day dsRed+ hESC-CMs, and its densities increased from -1.2 +/- 0.6 pA/pF at -120 mV and 3.6 +/- 1.0 pA/pF at 60 mV by 6- and 2-folds, respectively. With higher [Ca(2+)](i), 7+90-day ventricular hESC-CMs spontaneously but irregularly fired transients upon a single stimulus under an external Na(+)-free condition; however, without extracellular Na(+), nifedipine could completely inhibit Ca(2+) transients. We conclude that I(NCX) is functionally expressed in developing ventricular hESC-CMs and contributes to their excitation-contraction coupling.

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